Does Diabetes Always Confer Coronary Heart Disease Risk Equivalent to a Prior Myocardial Infarction?

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Implications for prevention

The excess risk for future coronary heart disease (CHD) events attributable to diabetes alone in the absence of coexisting CHD was not well understood until the publication by Haffner et al. (1) on this subject in 1998, which concluded that the elevation in risk was essentially similar to nondiabetic individuals with a prior myocardial infarction. This conclusion was based on a nonsignificant adjusted hazard ratio of 1.2 for CHD mortality over 7 years of follow-up in a Finnish cohort. This article had a considerable impact on our thinking and approach to CHD prevention in diabetes given its publication in a prestigious medical journal and high number of citations since (n = 3,676; scholar.google.com, accessed 4 October 2010). It provided justification for taking the same intensive approach to CHD prevention as used in individuals with a prior myocardial infarction, including aspirin as a cornerstone of treatment. In apparently equivalent high-risk states of diabetes and prior CHD, the benefit of aspirin in reducing risk of myocardial infarction has been believed to outweigh uncommon bleeding complications and yield a net average expected benefit. Given the finding of Haffner et al. and previous American Diabetes Association (ADA) recommendations in favor of the use of aspirin to prevent CHD in many individuals with diabetes, why then would a recent ADA position statement change course by recommending more limited aspirin use based on overall cardiovascular disease (CVD) risk (2,3)?

A number of reasons seem to justify this change in recommendations. There have been major advances in treatment approaches to type 2 diabetes, replications of the finding by Haffner et al. are inconsistent, and recent data suggest that the utility of aspirin for CHD prevention may be of a lesser magnitude than previously believed. First, it should be pointed out that even though the article by Haffner et al. was published in 1998, the data used for this analysis were generated in Finland between 1982 and 1990 (1). This was the pre-Diabetes Control and Complications Trial (DCCT) and pre-UK Prospective Diabetes Study (UKPDS) era, and the mean fasting glucose value of 210 mg/dL in individuals with diabetes and no CHD history in the Finnish cohort reflects this fact, and this value would be inconsistent with the level of glucose control currently recommended (4–6). Also, all diabetic subjects were medication treated, thereby representing a group with greater disease burden than would be seen in all individuals with diabetes, including those maintained on lifestyle therapy. Third, presence of prior CHD was sought only in individuals who reported a previous hospital admission for evaluation of chest pain. Given that diabetes is known to be associated with a higher frequency of silent myocardial infarction, this strategy may have resulted in misclassification of past myocardial infarction. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study demonstrated that over a third of new cases of myocardial infarction that occurred during this trial in individuals with diabetes were silent (7). It is likely, therefore, that the diabetic group without CHD did in fact contain a substantial unknown number of individuals with silent CHD. This proportion was likely further increased by poorer glycemic control—a known modifiable predictor of CHD risk as learned from both the DCCT and UKPDS clinical trials (8,9). If these individuals had been excluded and correctly classified, the risk for future CHD among the diabetic group would have certainly been lower.

Perhaps not surprisingly, attempts to replicate the finding of Haffner et al. have for the most part been unsuccessful. A recent meta-analysis of studies comparing CHD risk in individuals with diabetes with those with prior myocardial infarction but without diabetes reported significantly lower overall relative odds of CHD events in the individuals with diabetes (10). A total of 13 studies comprising 45,108 patients met the inclusion and exclusion criteria for this meta-analysis, with a calculated overall odds ratio for fatal or nonfatal myocardial infarction of 0.56 (95% CI 0.53–0.60) comparing individuals with diabetes alone with those with prior myocardial infarction and without diabetes (10). Of the 13 studies included, 11 reported significantly lower odds of incident CHD among individuals with diabetes (10). In addition, another recent prospective study conducted in Spain found a hazard ratio of 0.33 for fatal or nonfatal myocardial infarction in individuals with type 2 diabetes compared with nondiabetic individuals with a prior myocardial infarction (11). In most populations, it now seems safe to conclude that diabetes is not the equivalent of prior myocardial infarction with respect to future risk of CHD.

Diabetes need not be a CHD equivalent to merit prophylactic aspirin treatment to prevent myocardial infarction if the potential benefits of this preventive treatment outweigh the risks. The ADA committee that recently evaluated this subject performed a meta-analysis that incorporated the most recent aspirin clinical trial data among patients with diabetes to assist with their decision. The overall risk ratio of CHD events for the nine studies included was 0.91 (95% CI 0.79–1.05), consistent with no significant reduction in risk of these outcomes with aspirin use (3). A similar nonsignificant result was seen with regard to prevention of stroke with aspirin. Furthermore, aspirin use was not as safe as previously presumed. Rates of extracranial bleeding complications appeared to be ~50% higher among individuals with diabetes compared with those without in the Antithrombotic Trialists' Collaboration meta-analysis (12).

Given concerns about the miniscule magnitude of benefit and the moderate potential for bleeding complications in individuals with diabetes, the 2010 ADA position statement recommended more limited use of aspirin than previously advised in 2007 (2). The current statement recommends aspirin for individuals with diabetes whose CVD risk exceeds 10% and who are not at higher risk for gastrointestinal bleeding (3). Diabetic individuals at this level of elevated CVD risk would generally include men over age 50 years and women over age 60 years with one or more additional major CVD risk factors (hypertension, smoking, dyslipidemia, albuminuria, and family history of CVD), although treatment of these risk factors may lower the CVD risk level to less than 10%. Aspirin was not recommended for diabetic men aged 50 years and younger and women aged 60 years and younger without additional CVD risk factors. Formerly, the ADA recommendation included aspirin treatment for individuals with diabetes over age 40 years or with any additional CVD risk factor, but not for individuals younger than age 21 years because of concerns about risk of Reyes syndrome (2).

One could argue as to why aspirin use was recommended at all for individuals with diabetes given the lack of clearly demonstrated benefit. We think that the counterargument is that definitive research to rule out a benefit has not been performed, and that currently available data suggest a small but as yet unproven effect that can be balanced against potential harms for individual patients.

The 2010 ADA position statement on aspirin use recommends risk estimation in making the decision to prescribe treatment and refers readers to several currently available models including the UKPDS Risk Engine, the Atherosclerosis Risk in Communities (ARIC) CHD Risk Calculator, and the ADA Diabetes Personal Health Decisions (PHD) (3). It is likely that we will increasingly be using such estimation for more personalized clinical medicine in the future. The proliferation of prediction models permits assessment of risk with much less granularity than has been available previously. Furthermore, the progress of genomics and personalized medicine has the potential to lead to significant advances in pharmacogenetic profiling to predict the effectiveness or risks of specific medication treatment or for prevention (13). Such developments hold promise for the application of treatments with benefits that more likely outweigh risks.

The equating of diabetes to prior myocardial infarction in terms of future CHD risk by Haffner et al. seems to be one reason that their article generated enormous interest in the subject. The *New England Journal of Medicine* (NEJM) article by Haffner et al. has received more citations than the 3,267 received by the 2002 NEJM article from the Diabetes Prevention Program reporting the benefits of a lifestyle intervention or metformin in preventing diabetes in individuals at higher risk (scholar.google.com, accessed 8 October 2010) (14). Would the article have received the same degree of interest if the results were presented numerically instead as 20.2 incident cases per 100 person-years for diabetes present, prior CHD absent compared with 18.8 per 100 person-years for diabetes absent, prior CHD present? We think not. Framing refers to the presentation of identical risk information in different ways and has been shown to affect judgment and choices (15). The analogy drawn between diabetes and heart disease makes it immediately apparent that CHD risk is seriously elevated in diabetes, an observation very familiar to health care providers. Interpretation of risk information conveyed as relative risks, absolute risks, or other quantitative measures has been shown to be inconsistent, and at times incorrect, even by individuals with excellent numeracy skills (16). One can also reframe the risks of aspirin use by comparing it with a more familiar experience. This has been done only once to our knowledge, and it was concluded that using aspirin is about as dangerous as driving in a car as judged by similarity of fatality rates (17). Alternatively one can examine the point at which aspirin-related adverse events would occur more frequently than CVD occurrences prevented. This would be expected when the annual CVD risk is 1% or less (3). Whether reframing of the risk of aspirin use in these terms would lead to greater or lesser enthusiasm for its use has not been examined.

The quest for the best approaches to prevent vascular complications in individuals with diabetes is a continuing pursuit. The recent change in ADA recommendations seems well justified by continuing progress in our understanding of the magnitude of excess CHD risk in individuals with diabetes and the benefits and risks of aspirin treatment.

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